

Radiation Epidemiology Course
May 16-20, 2011

Cancer Risk and Radon Exposure

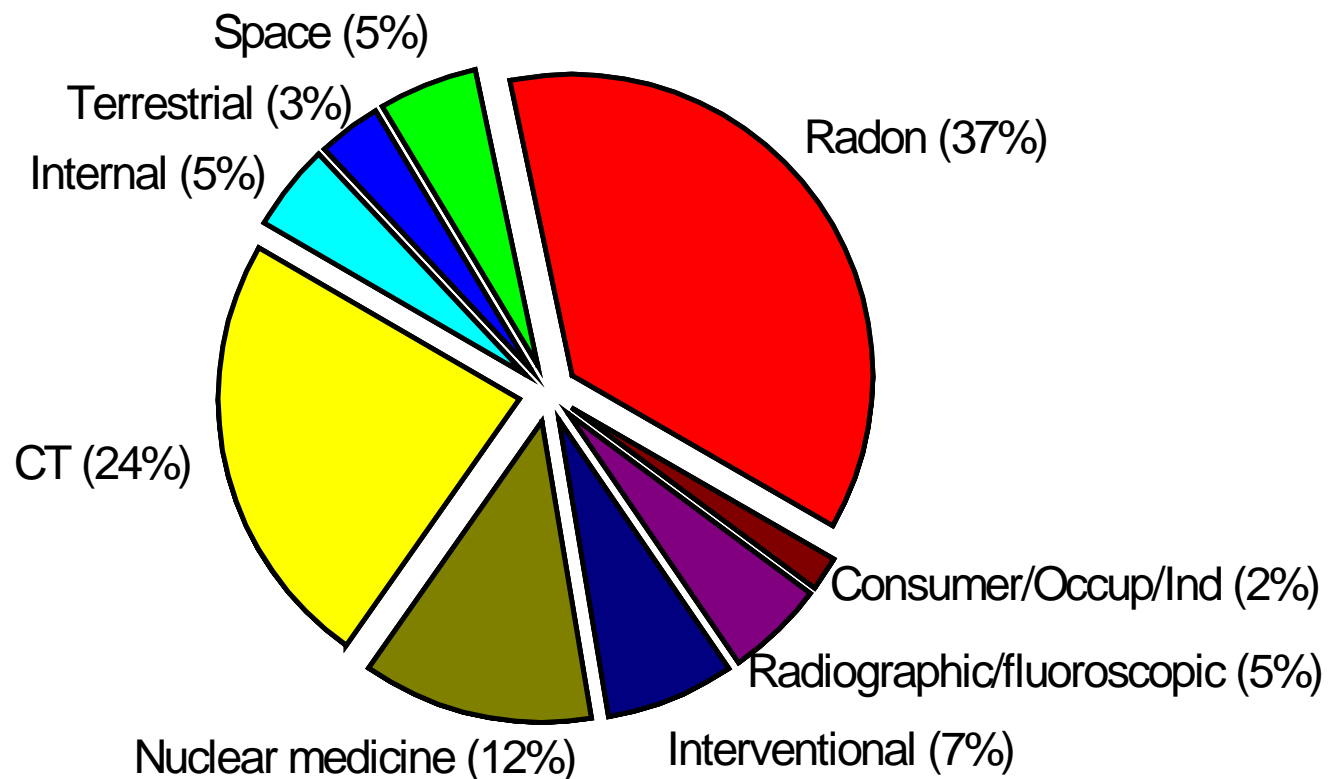
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Radon Exposure and Risk of Lung and Other Cancers

- Background
- Studies of underground miners
- Studies of radon in houses
- Public health burden
- Unanswered questions

Annual Per Capita Effective Dose (mSv)

Natural and Human Sources



NCRP, 2009

What is radon (^{222}Rn)?

- Noble gas
- Decay product of ^{238}U and ^{226}Ra
- Alpha emitter
- Rn half-life is 3.8 d
- High LET radiation

238

Uranium
4.5By

Mass
No
226

Radium
1620y

 α

222

Radon
3.82d

 α

218

Polonium
3.05m

 α

214

Lead
26.8m

 β

Bismuth
19.7m

 β

Polonium
0.00016s

 α

210

Lead
22y

Primary Radon Decay Chain

Short-lived
Rn progeny

Radon & Cancers Other Than Lung (Miners)

<u>Leukemia</u>	Pooled miner data	Darby JNCI 1995	N
(γ vs α):	E. Germany	Mohner AJIM 2006	N
	E. Germany	Dufey Hlth Phy 2011	N
	Czech (Pribram)	Rericha EPH 2006	Y *
	Czech (W Bohemia)	Tomasek Hlth Phy 2004	N
	Eldorado (Canada)	Lane Rad Res 2010	N

Non-lung solid tumors

Pooled miner data	Darby JNCI 1995	N
Czech (Pribram)	Kulich Environ Res 201	N
Eldorado (Canada)	Lane Rad Res 2010	N

Radon & Cancers Other Than Lung (Gen Pop)

Stomach: NRC, Radon in Water, 1999

Leukemia:

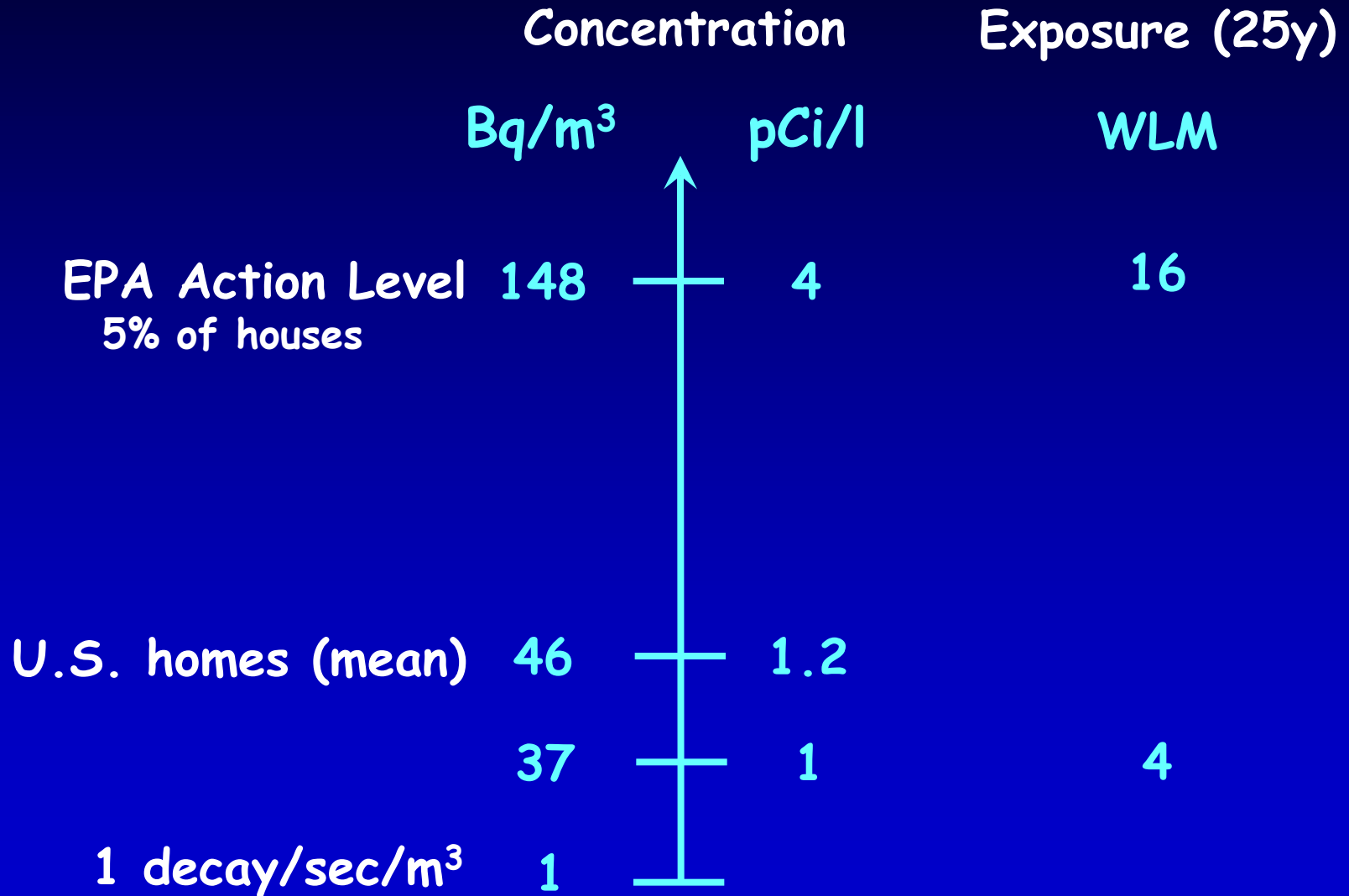
<u>Adults:</u>	Iowa (eco)	Smith Stat Med 2007	N
<u>Children:</u>	ALL (c/c study)	Lubin JNCI 1998	N
	UK (c/c study)	UK-CCS 2002	N
	Denmark (c/c study)	Raaschou-Nielsen Epi 2008	Y*
	Lower Saxony (c/c)	Kaletsch Rad Env Bio 1999	N
	France (eco)	Evrard Eur J Ca Prev 2005	y
	UK (eco)	Henshaw BJC 1990	y

Radon and Radon Decay Products and Lung Cancer

Units of Concentration/Exposure

- Mines: Rn and Rn progeny
 - 1 WL: 1.3×10^5 MeV of α energy from short-lived decay products
 - Working Level Months (WLM):
$$\sum WL_i \times \text{dur}_i \quad (\text{dur in units of 170 hrs})$$
 - 1 WL = 2.08×10^{-5} J/m³; 1 WLM = 3.5×10^{-3} Jh/m³
 - Mine standard: maximum 1 WL or 4 WLM/yr
- Residential studies:
 - 1 becquerel/m³ = 1 decay/sec/m³ (SI units)
 - 1 Curie/l = 3.7×10^{10} decays/sec/l (old units)
 - 37 Bq/m³ = 1 pCi/l = 0.01 WL (at equilibrium)

Measuring Radon in Homes



Computing Exposure in Houses

1 yr @ 37 Bq/m³ (at equilibrium):

$$0.01 \text{ WL} \times (365 \times 24 / 170) = 0.52 \text{ WLM/yr}$$

and @ 40% equilibrium:

$$0.01 \text{ WL} \times (365 \times 24 / 170) \times 0.40 = 0.21 \text{ WLM/yr}$$

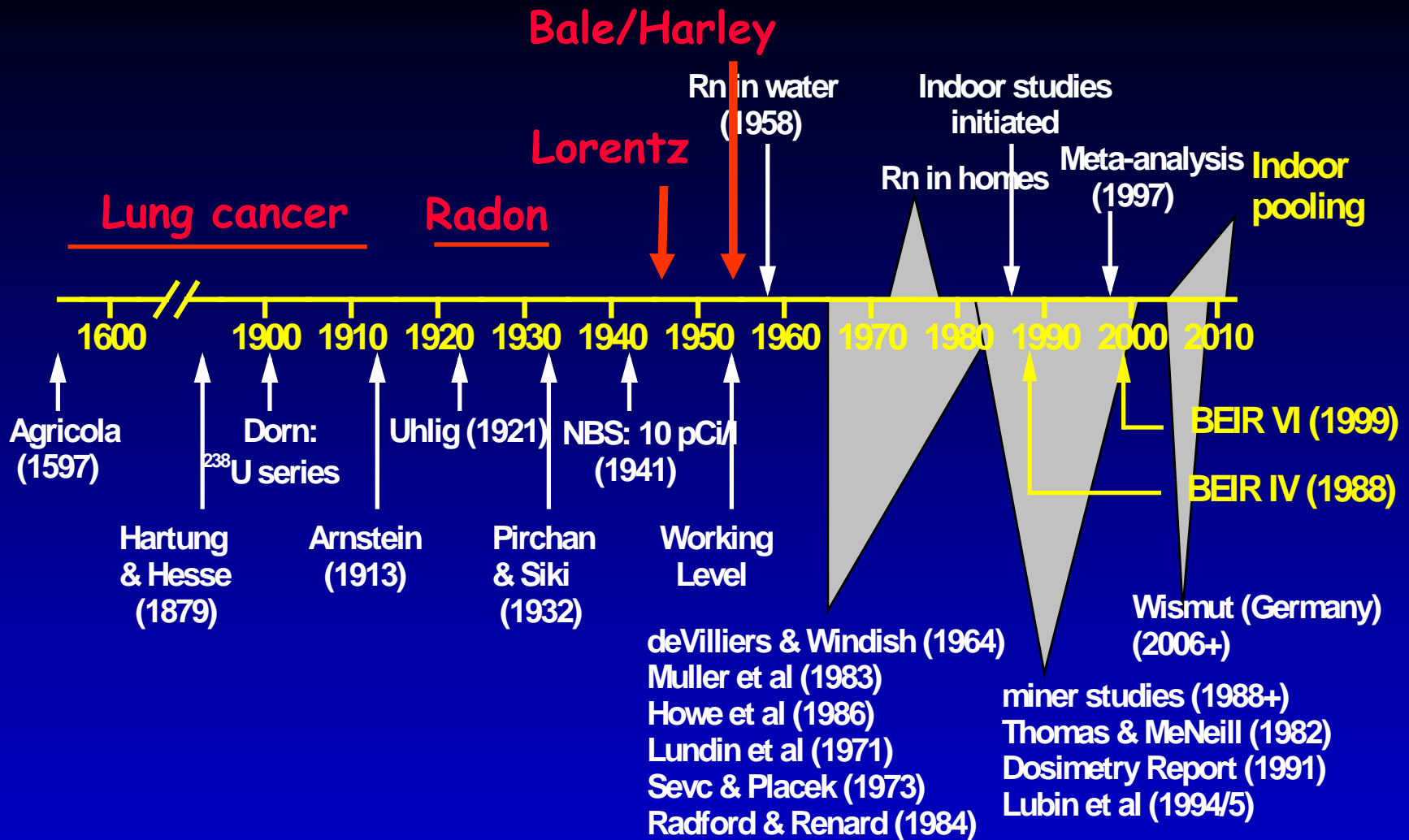
and with 75% occupancy:

$$0.01 \text{ WL} \times (365 \times 24 / 170) \times 0.40 \times 0.75 = 0.15 \text{ WLM/yr}$$

for a 25y exposure period:

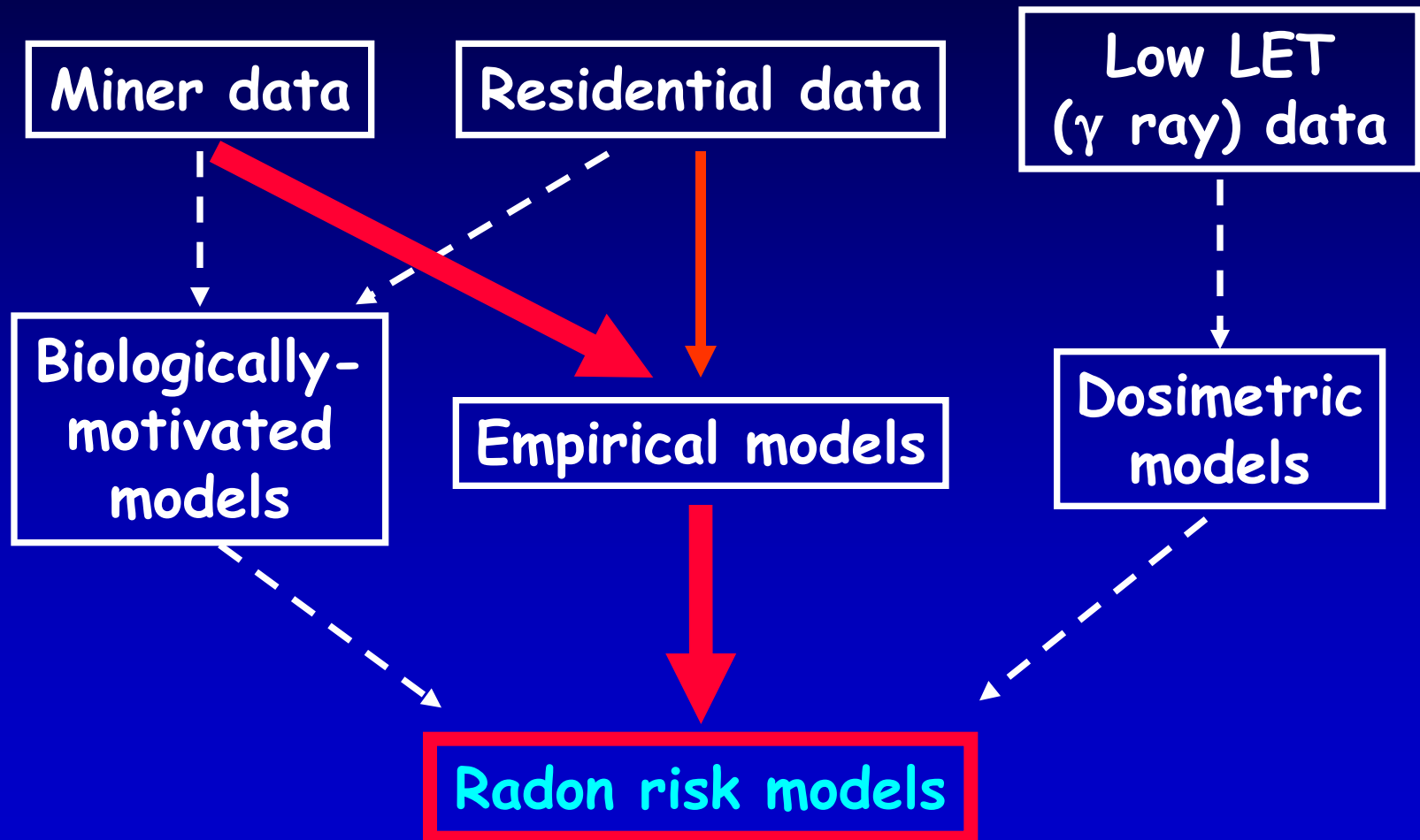
$$0.01 \text{ WL} \times (365 \times 24 / 170) \times 0.40 \times 0.75 \times 25 = 3.9 \text{ WLM}$$

Residing 25 yr @ 37 Bq/m³ \approx 3 - 5 WLM



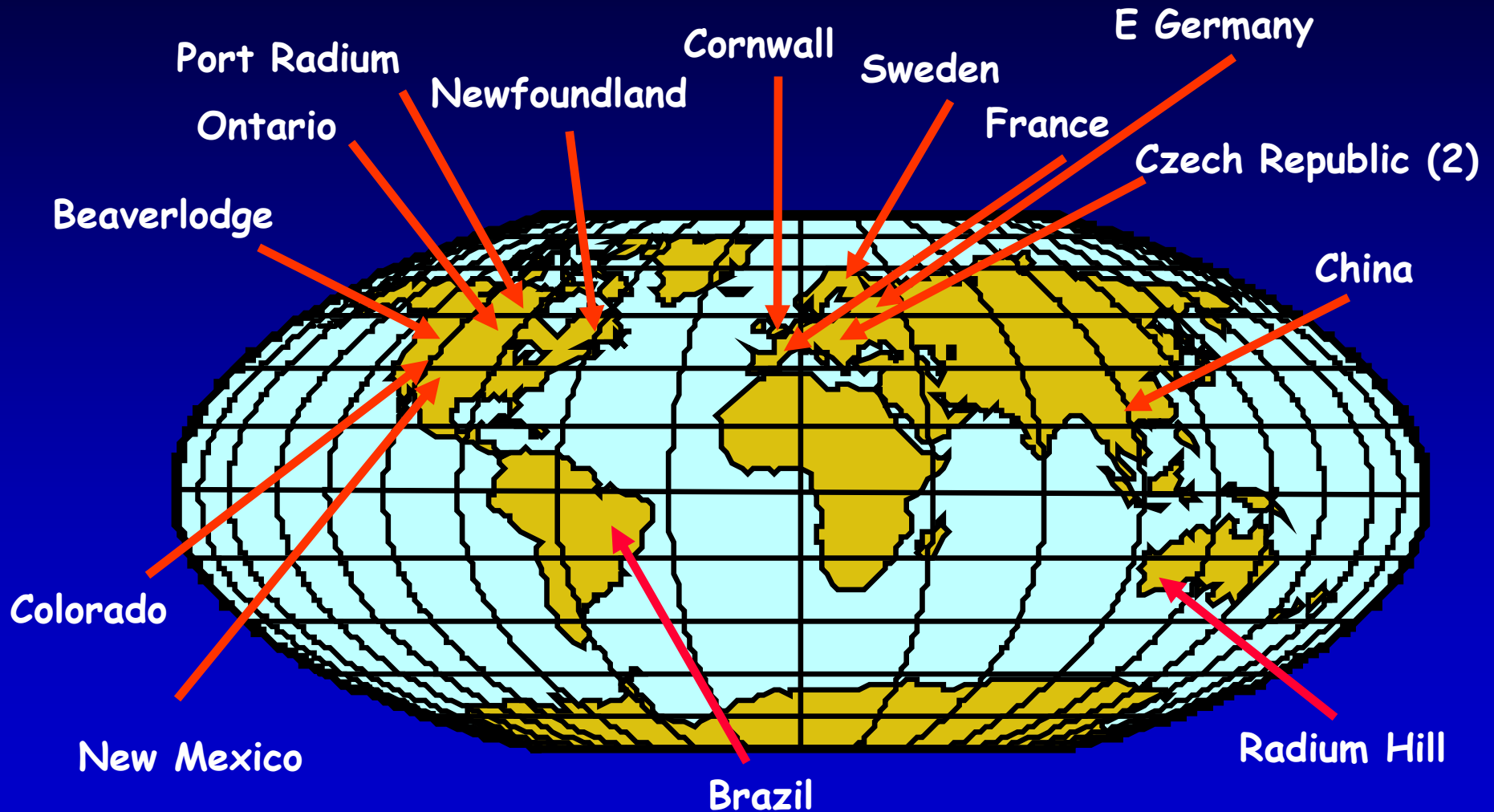
Chronology of Important Radon Events

Generating Risk Estimates for Exposure to Radon



Studies of Underground Miners

Studies of Radon-Exposed Miners





Pooled Analysis of Miners

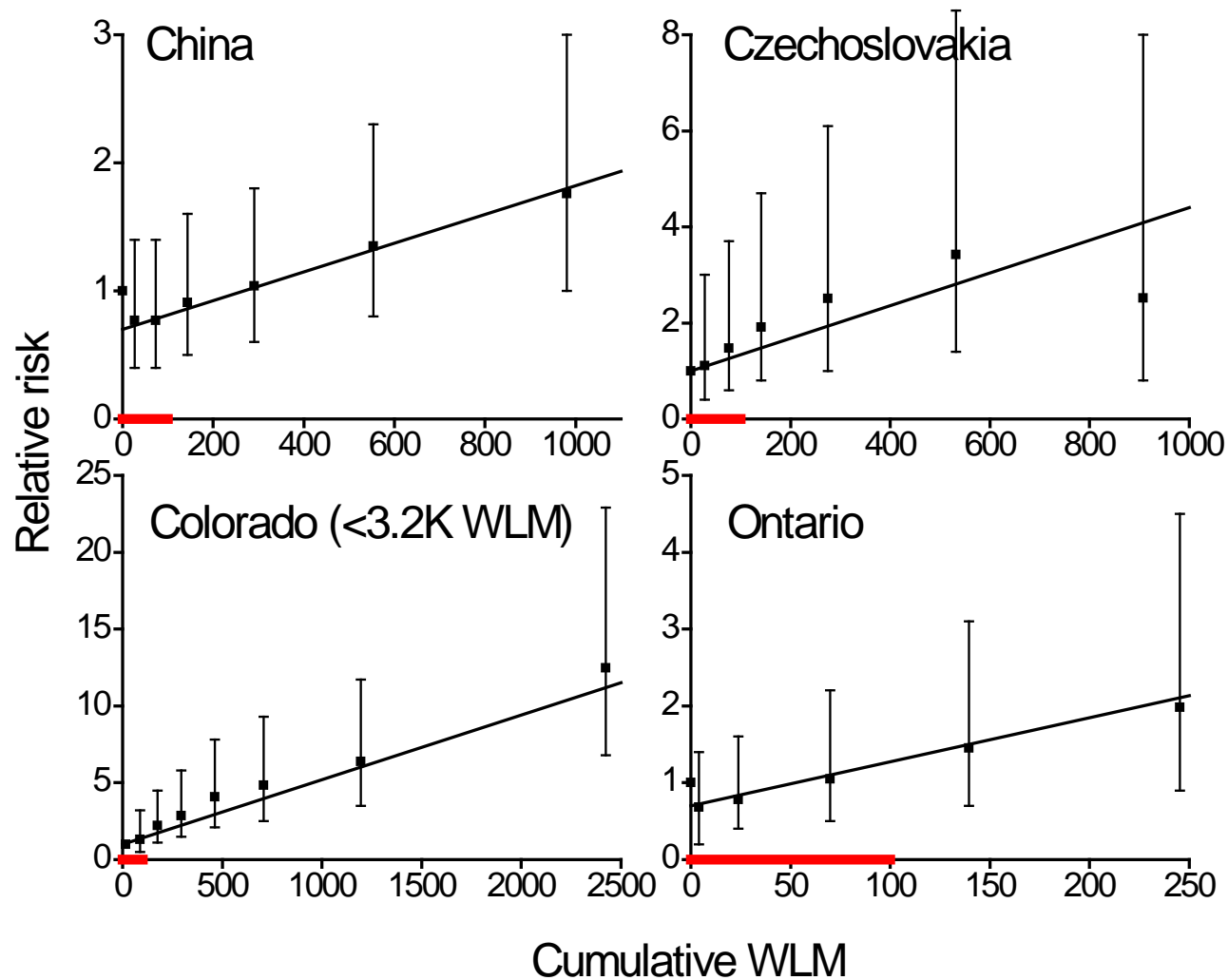
Study	Lung ca	P-yrs
China *	980	175,342
Czech Republic	705	106,924
Colorado *	336	87,821
Ontario	291	380,719
Newfoundland *	118	48,742
Sweden *	79	33,293
New Mexico *	69	55,964
Beaverlodge	65	118,385
Port Radium	57	52,677
Radium Hill *	54	51,624
France	45	43,962
Total	2,787	1,155,453

Mean: WLM = 164, WL=2.9, Dur=5.7 y

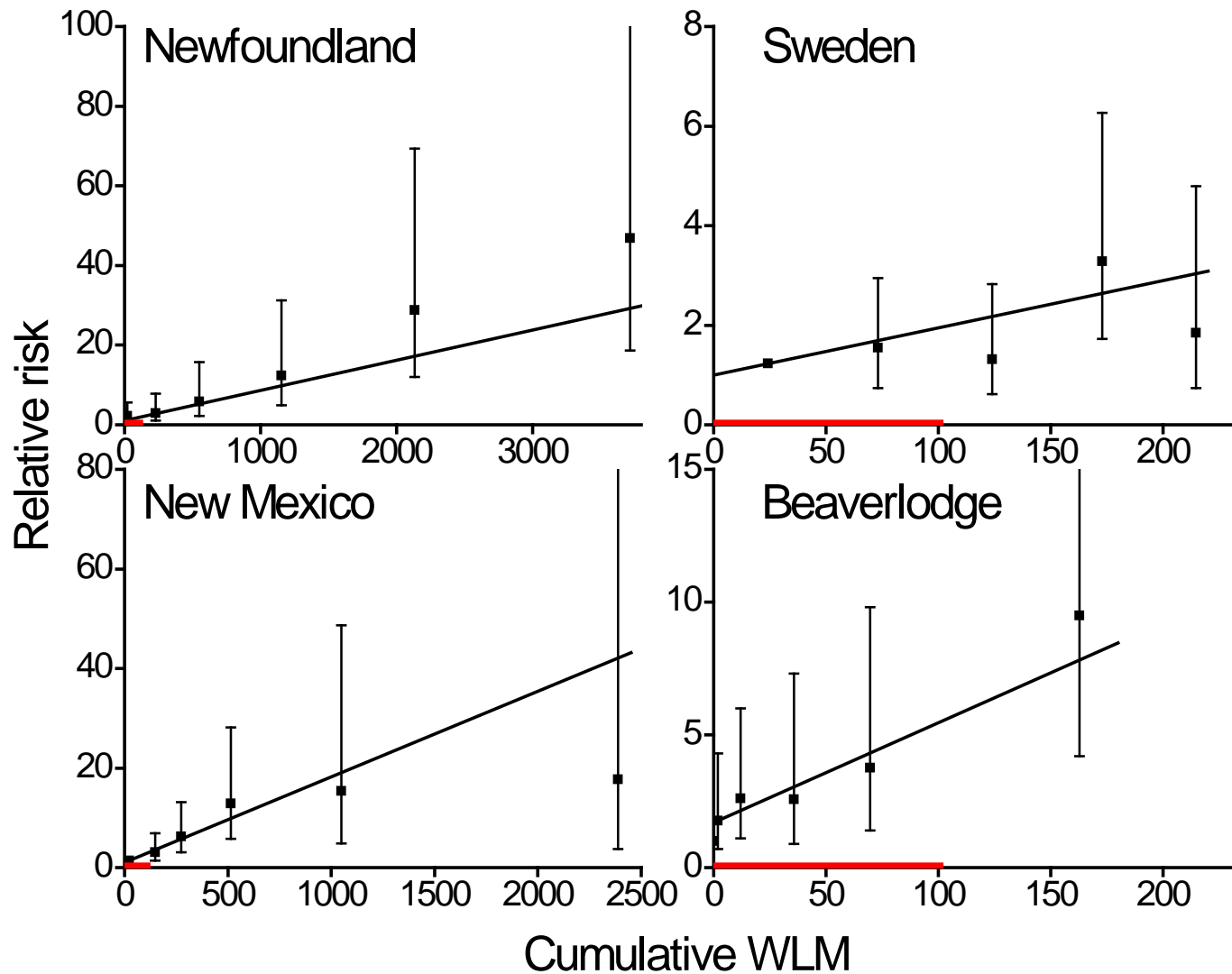
* Cohorts with smoking info

Lubin et al 1995
BEIR VI, 1999¹⁷

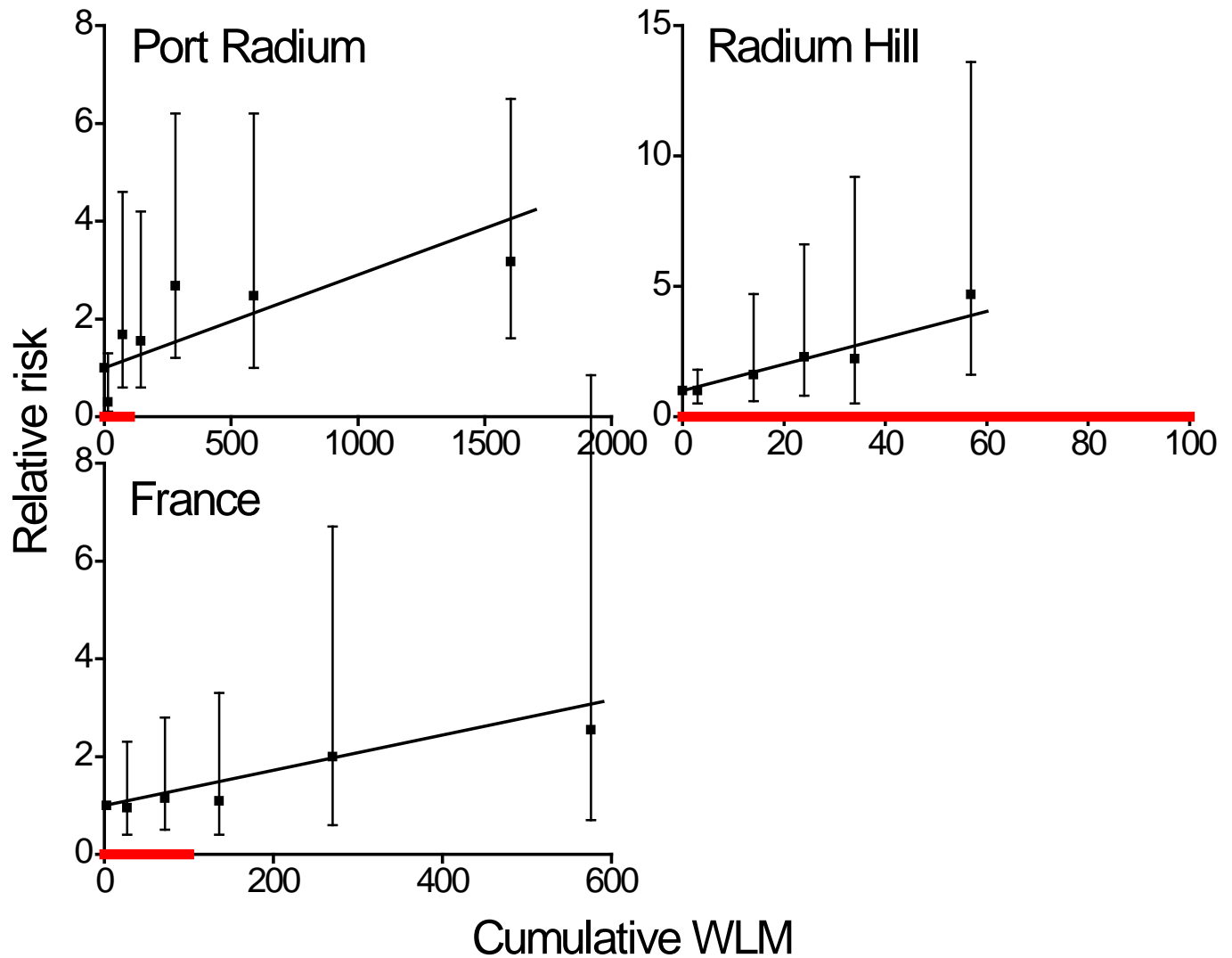
Dose-Response in Miner Studies (I)



Dose-Response in Miner Studies (II)



Dose-Response in Miner Studies (III)



Risk models for Lung Cancer (NAS 1999)

Exposure-age-duration model:

$$RR = 1 + \beta(\text{age}, \text{dur}) \times WLM^*$$

Exposure-age-concentration model:

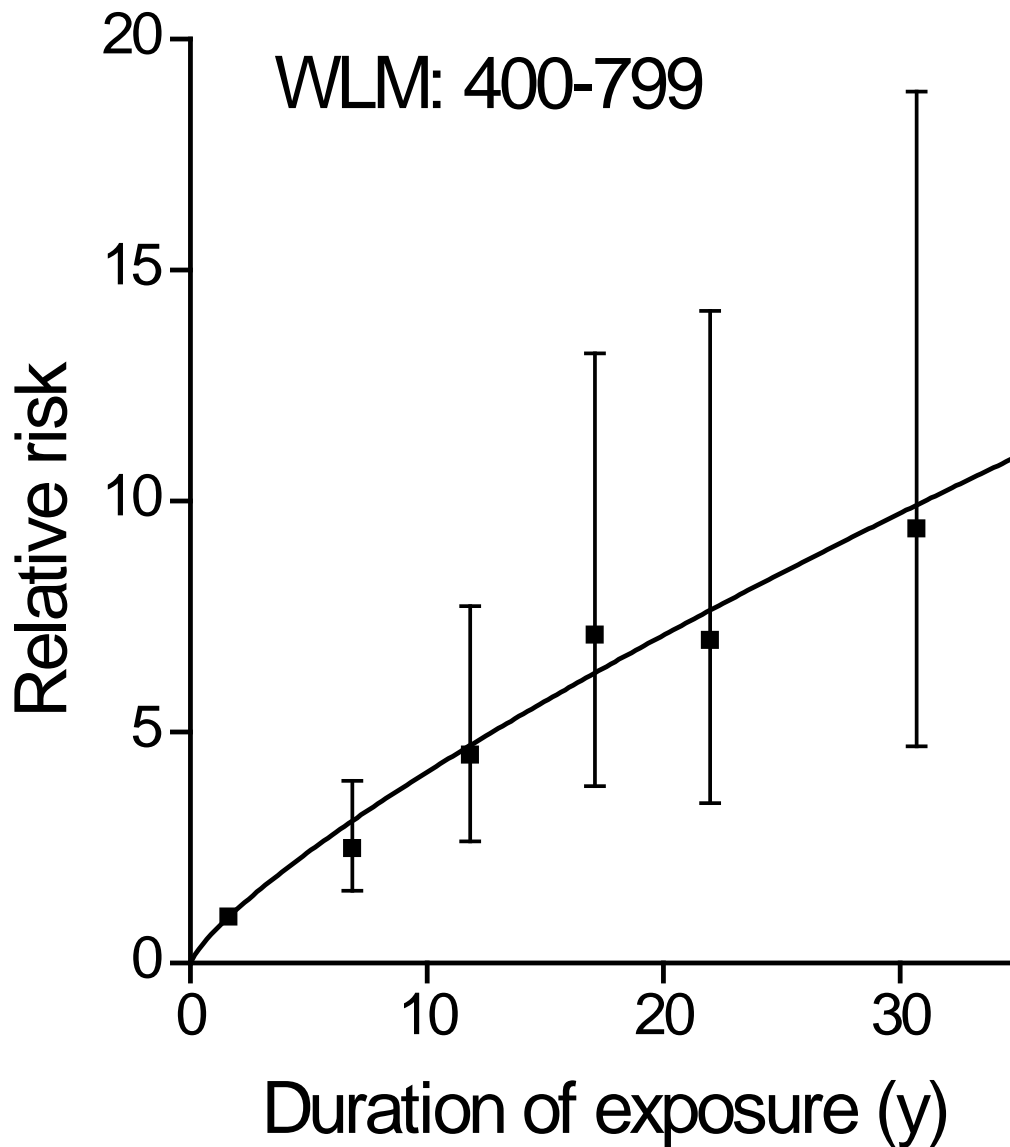
$$RR = 1 + \beta(\text{age}, WL) \times WLM^*$$

WLM^* = WLM weighted by time since exposure
Smokers: $0.9 \times \beta$; never-smokers: $2.0 \times \beta$

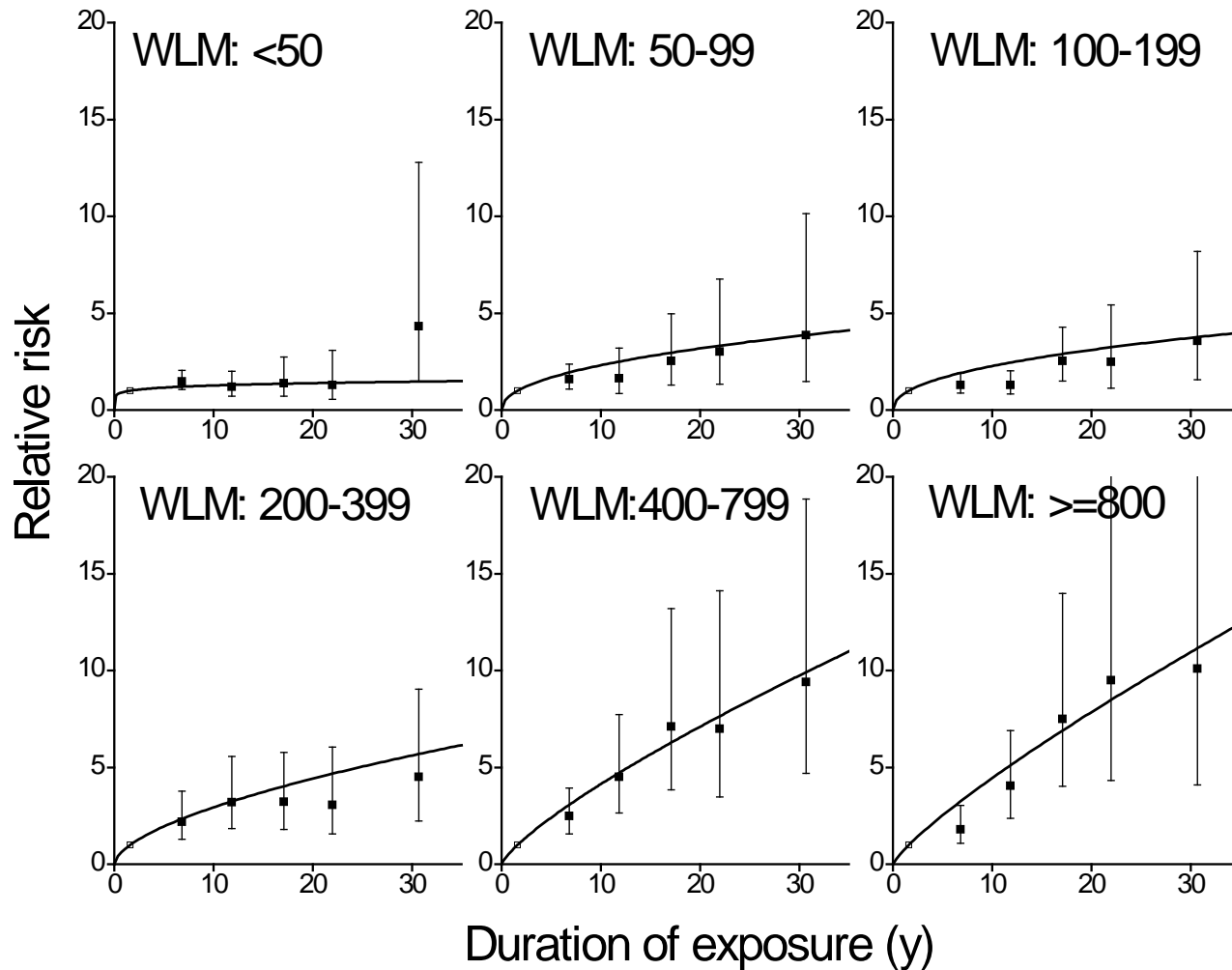
Time Since Exposure Effects

$$WLM^* = 1.0 \times W_{5-14} + 0.8 \times W_{15-24} + 0.5 \times W_{25+}$$

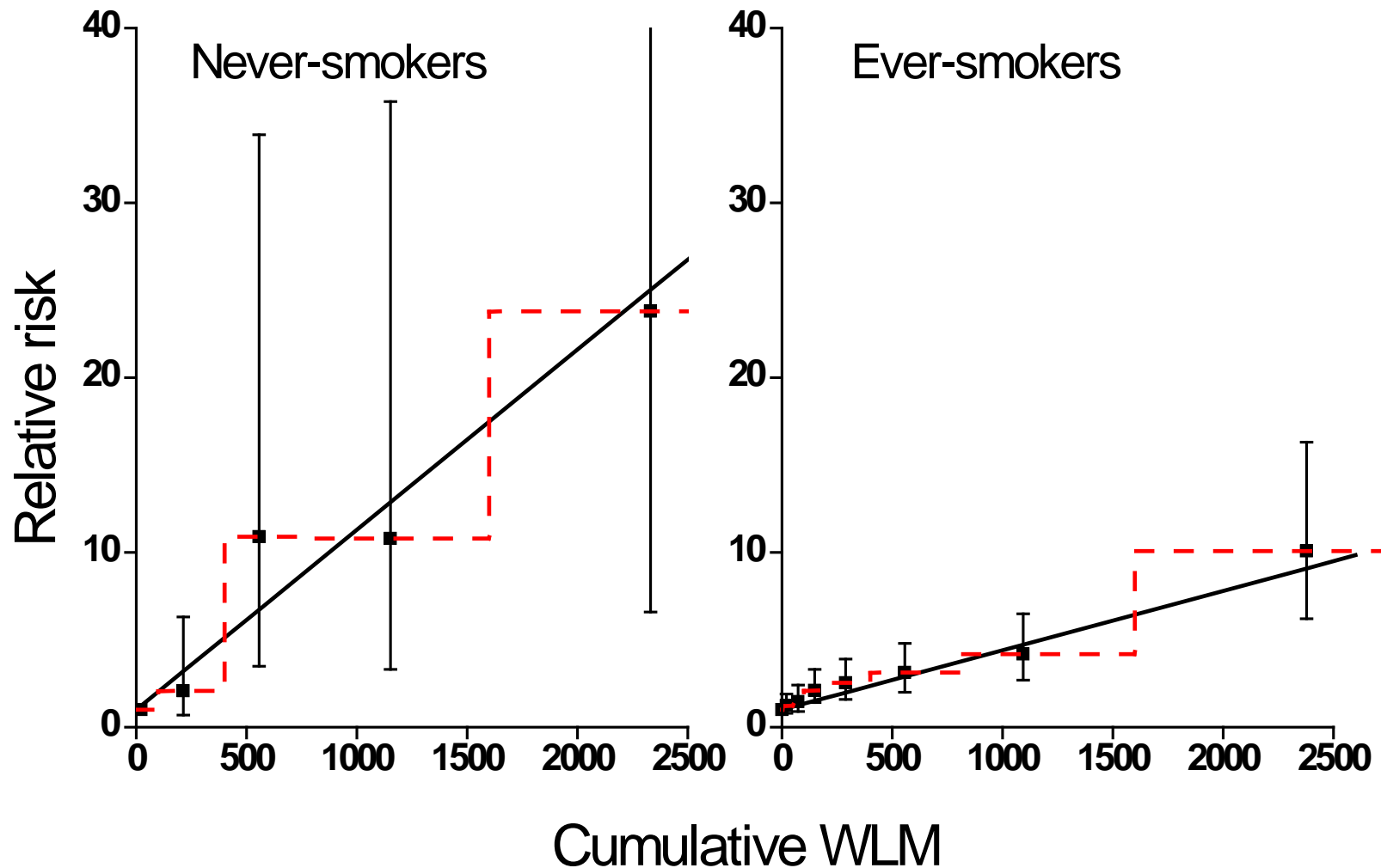
RR Patterns and the Inverse Dose-Rate Effect



The Inverse Dose-Rate Effect for Radon



RRs for Ever/Never Smoking Miners



Additional Lung Cancer Studies Since BEIR VI

- Czech miners
 - West Bohemia: lung cancer; Tomasek, Rad Res 1999
- French miners
 - Laurier, Eur J Epi 2004; Rogel, J Rad Prot 2002
- Newfoundland fluorspar miners
 - Villeneuve, Health Phys 2007
- Beaverlodge & Port Radium (Canada)
 - Lane, Rad Res 2010
- Brazilian coal miners
 - Veiga, Radiat Env Biophys 2006
- GDR miners (Wismut)
 - Grosche, BJC 2006; Kreuzer, Rad Env Biophy 2010; Walsh et al Rad Res 2010

BEIR VI & Wismut: Exposure-Age-Conc model

	Lung Ca	WLM	Dur: yrs	max
BEIR VI:	2,787	164	6	55
Wismut:	3,016	280	14	44

$$RR = 1 + \beta \text{WLM}^* \varphi_{\text{age}} \varphi_{\text{WL}}$$

with $\text{WLM}^* =$

$$\text{WLM}_{5-14} + \theta_2 \text{WLM}_{15-24} + \theta_3 \text{WLM}_{25-34} + \theta_4 \text{WLM}_{35+}$$

$$RR = 1 + \beta WLM^* \phi_{age} \phi_{WL}$$

	RETD VT	Wismut	
	ERR/WLM	0.075	0.026
TSE	5-14	1.00	1.00
	15-24	0.78	0.71
	25-34		0.49
	35+	0.51	0.36
Age	<55	1.00	1.00
	55-64	0.57	0.46
	65-74	0.29	0.31
	75+	0.09	0.32
WL	<0.5	1.00	1.00
	0.5-0.9	0.49	0.61
	1.0-2.9	0.37	0.48
	3.0-4.9	0.32	0.43
	5.0-14.9	0.17	0.36
	15+	0.11	0.22

Lifetime RR (LR_e/LR_o) of Lung Cancer with US Rates

Bq/m ³	BEIR VI	Wismut
37	1.09	1.04
100	1.23	1.10
150	1.34	1.14
200	1.45	1.19
800	1.89	1.38

Equilibrium factor, 0.4; Occupancy, 70%; TSE, 5-45 yrs

Lifetime RR (LR_e/LR_o) of Lung Cancer for "Miners"

WLM/yr		
22	1.48	1.37

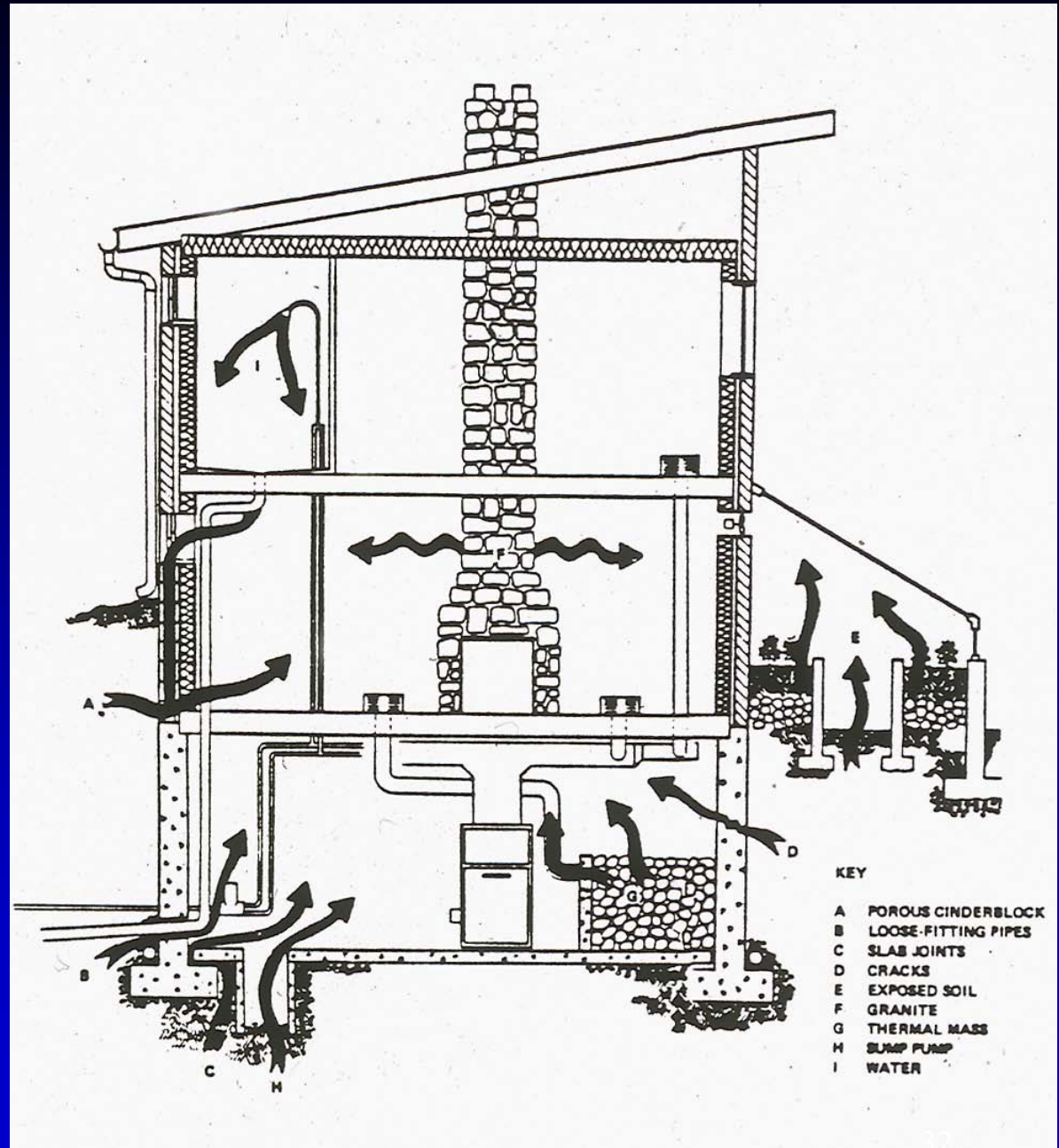
Duration = 10 yr

Residential Studies of Radon

Case-Control Studies of Lung Cancer and Residential Radon

- ❖ Compare residential risks with miner extrapolations
- ❖ Direct estimate of exposure-response relationship
- ❖ Evaluate other factors, e.g., females, children

Routes of Entry of Radon into Houses





Pooling of Residential Radon Studies

- ❖ Workshops (1989, 1991, 1995)
 - annual/semi-annual meetings 1995-2004
- ❖ North America/Europe/China
- ❖ World pooling

Pooling of Residential Radon Studies

	<u>No.</u>	<u>Cases</u>	<u>Controls</u>
N America	7	4,108	5,301
China	2	1,076	2,015
Europe	13	7,148	14,208
Total		12,332	21,524

Results of Indoor Rn studies: EOR at 100 Bq/m³

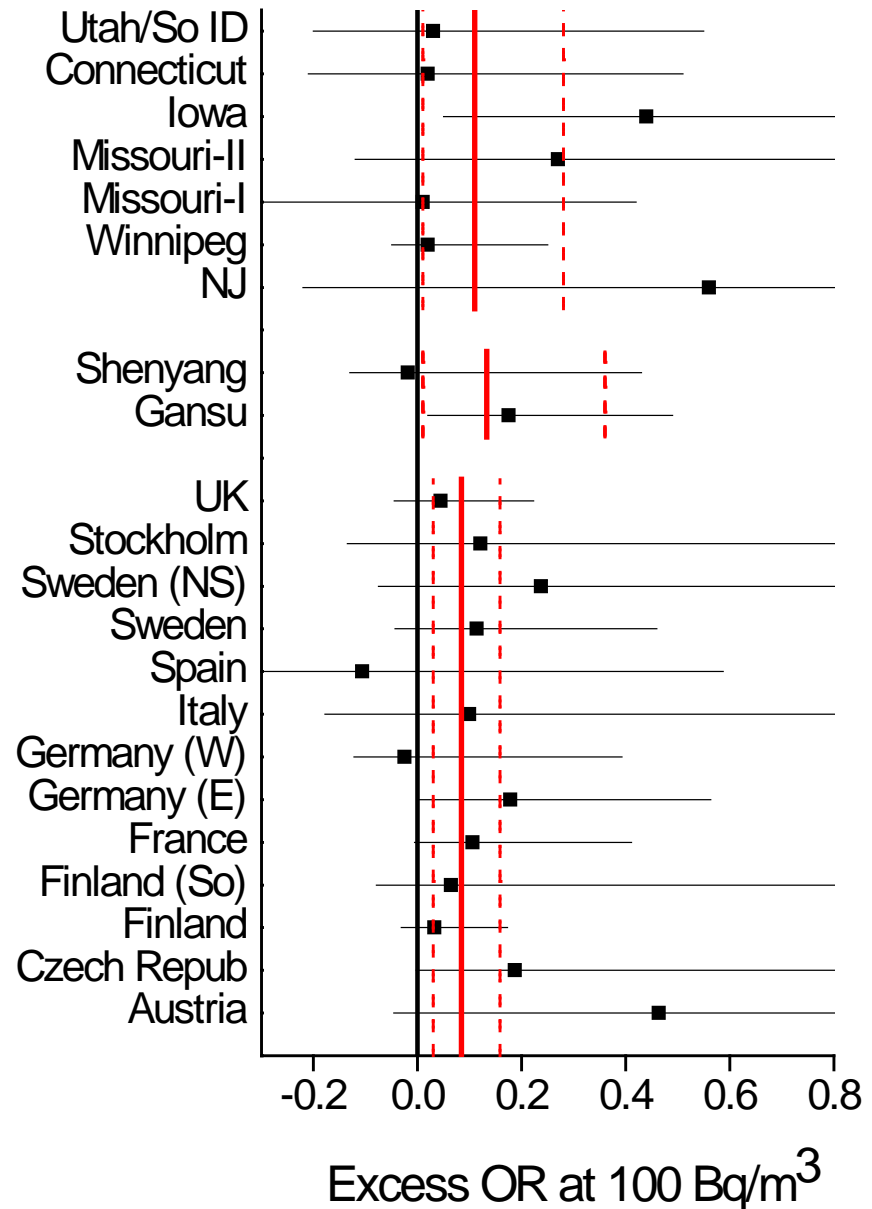
$$OR = 1 + \beta \times Bq/m^3$$

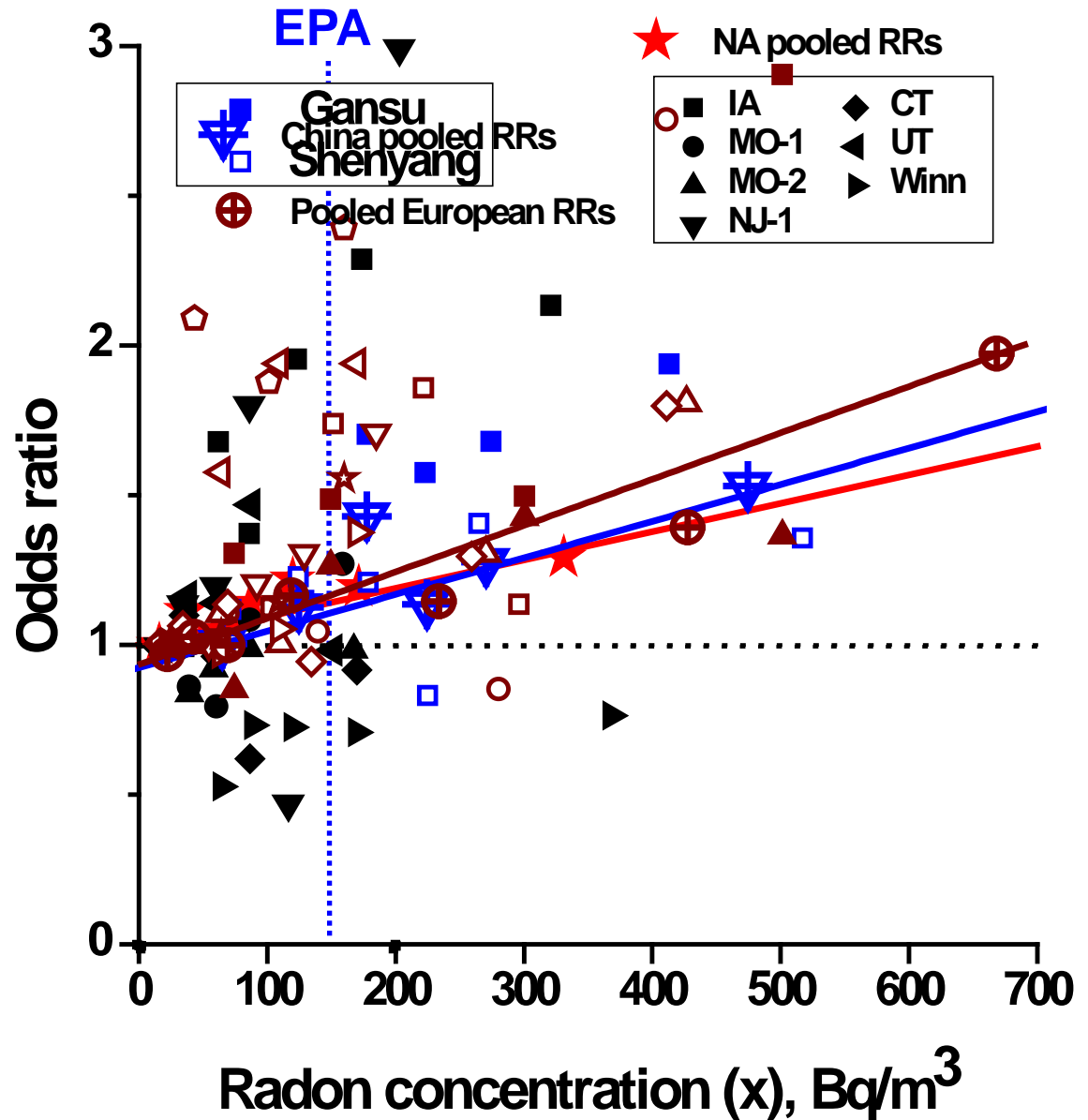
China: Lubin 2004

Eur: Darby 2004

NA: Krewski 2005

World: 2012





Attributable Risk of Lung Cancer

AR of Lung Cancer in the US from Indoor Radon

- Radon risk model
- Assumptions for residential extrapolation
- Radon concentration in US houses (EPA):
Log-Normal
 $GM = 24.8 \text{ Bq/m}^3$, $GSD = 3.1$
- Assume US mortality rates apply

U.S. EPA Assessment of Risks from Radon in Homes:

<http://www.epa.gov/rpdweb00/docs/assessment/402-r-03-003.pdf>

Assumptions for Extrapolating Risk from Miners to the General Population

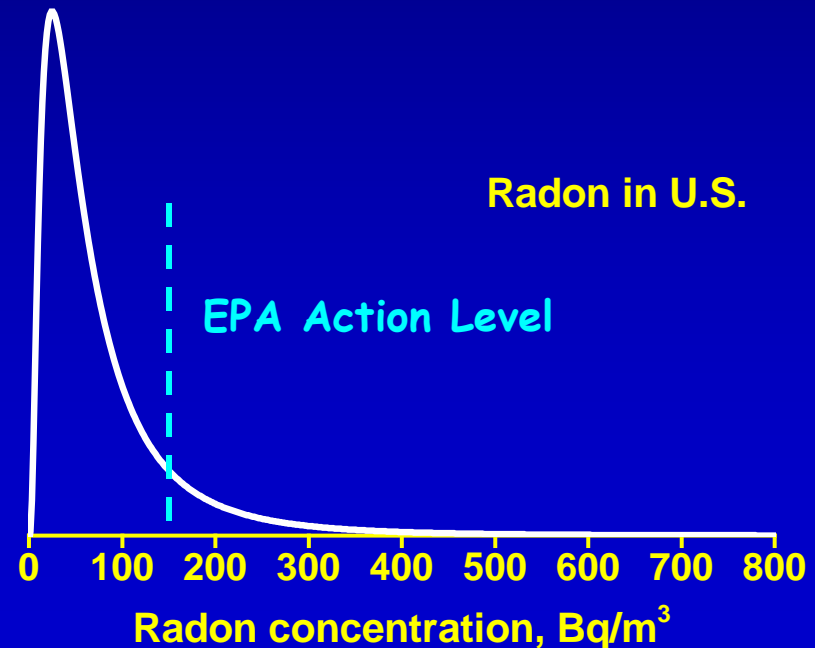
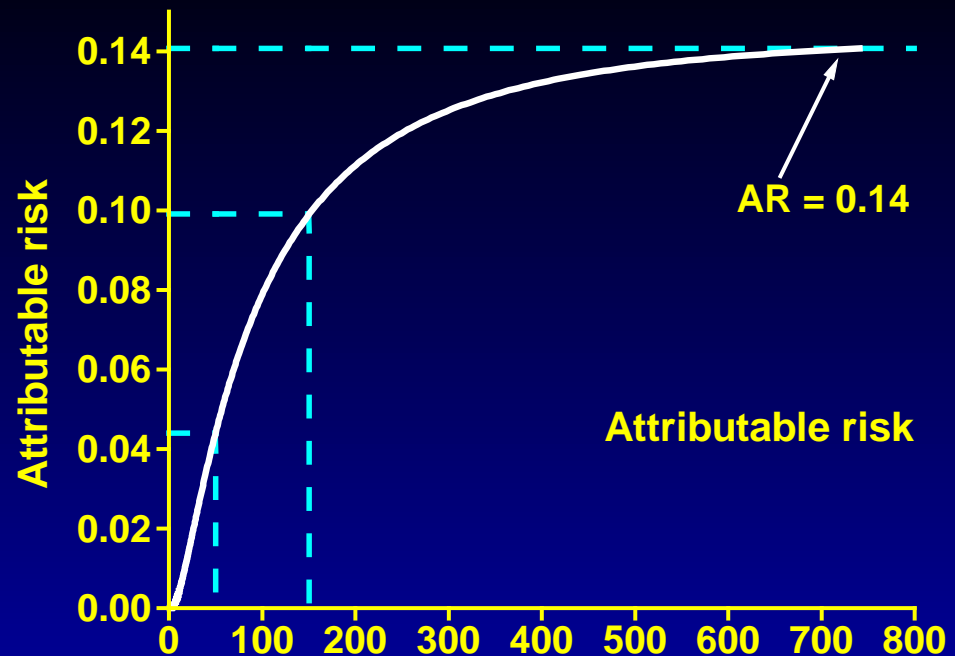
Factor	Assumption
Shape dose-response	Linear ERR
Exposure rate	Comparable risks for rates <0.5 WL or durations longer than 35 yr
Sex	ERR/exposure same in F and M
Age at exposure	ERR/exposure same for all ages
Cigarette smoking	Sub-multiplicative interaction: never-smokers - $2.0 \times \beta$ ever-smokers - $0.9 \times \beta$
Particle size/distn, activity, bronchial morphology	No modification, $K=1$
Other differences	ERR/exposure the same

Attributable Risk of Lung Cancer from Indoor Radon

	AR	Deaths/yr
Total	14%	20,500 (3,000-30,000)
Ever-smokers	12%	18,000
Never-smokers	23%	2,500

Cumulative AR for Radon

~ 1/3 from houses above EPA action level



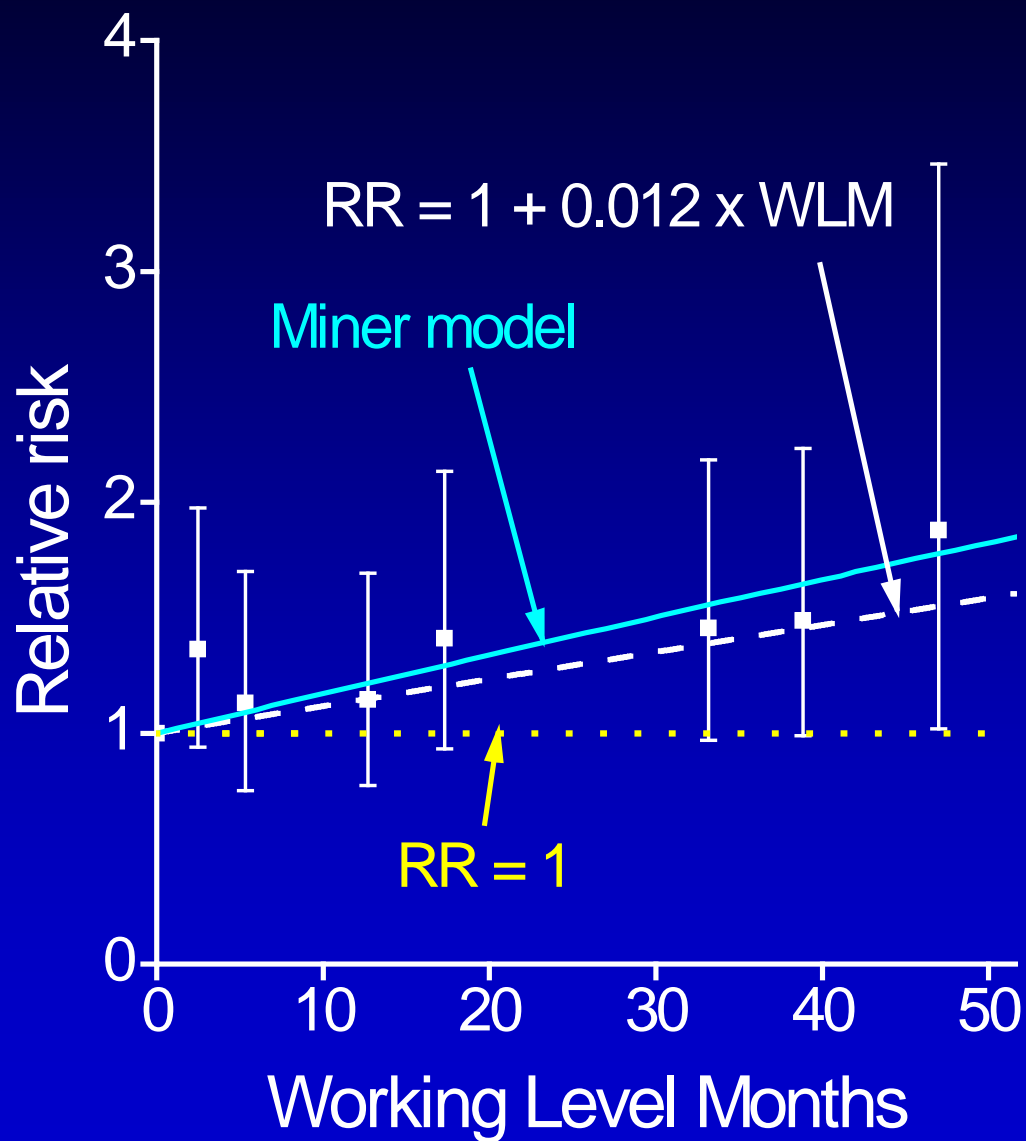
Attributable Risk for Radon

USA:	10-14% (3,000-30,000)	BEIR VI 1999
Missouri:	1-4%	Alavanja Envir Intl 1996
Canada:	7.8% (1,400)	Brand Risk Anal 2005
France:	2-12% (543-3,108)	Catelinois EHP 2006
Germany-W:	7% (500-8,200)	Steindorf IJE 1995
Germany:	2-13% (650-5,000)	Wichmann Epidemiol 2006
Europe:	9%	Darby BMJ 2004

Validity of Attributable Risk Estimates

- (1) Are miner-based models internally consistent for low-exposed miners?
- (2) Are miner-based models consistent with indoor Rn studies?
- (3) Is there radiobiological/epidemiological evidence for low-dose effects at indoor Rn levels?

RRs for Miner Exposures (<50 WLM)



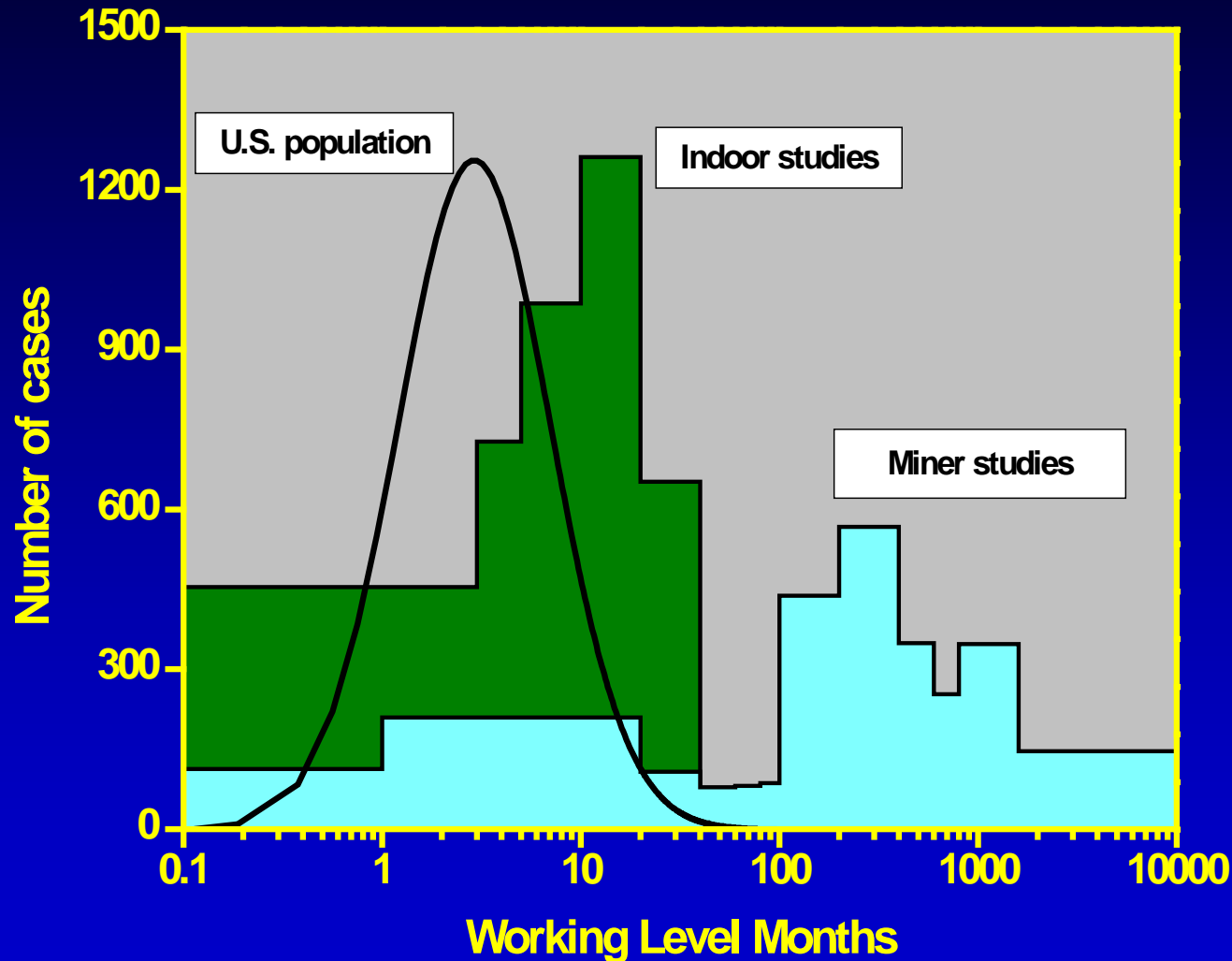
Models Fit to Restricted (<50 WLM) Miner Data

Model	Deviance	P for fit
Exp-age-dur (fixed)	1,753.8	
Exp-age-cond (fixed)	1,754.3	
Exp-age-dur (free)	1,751.3	0.87 \$
Exp-age-conc (free)	1,749.0	0.57 \$
$RR = 1 + \beta \times WLM$	1,754.2	0.52

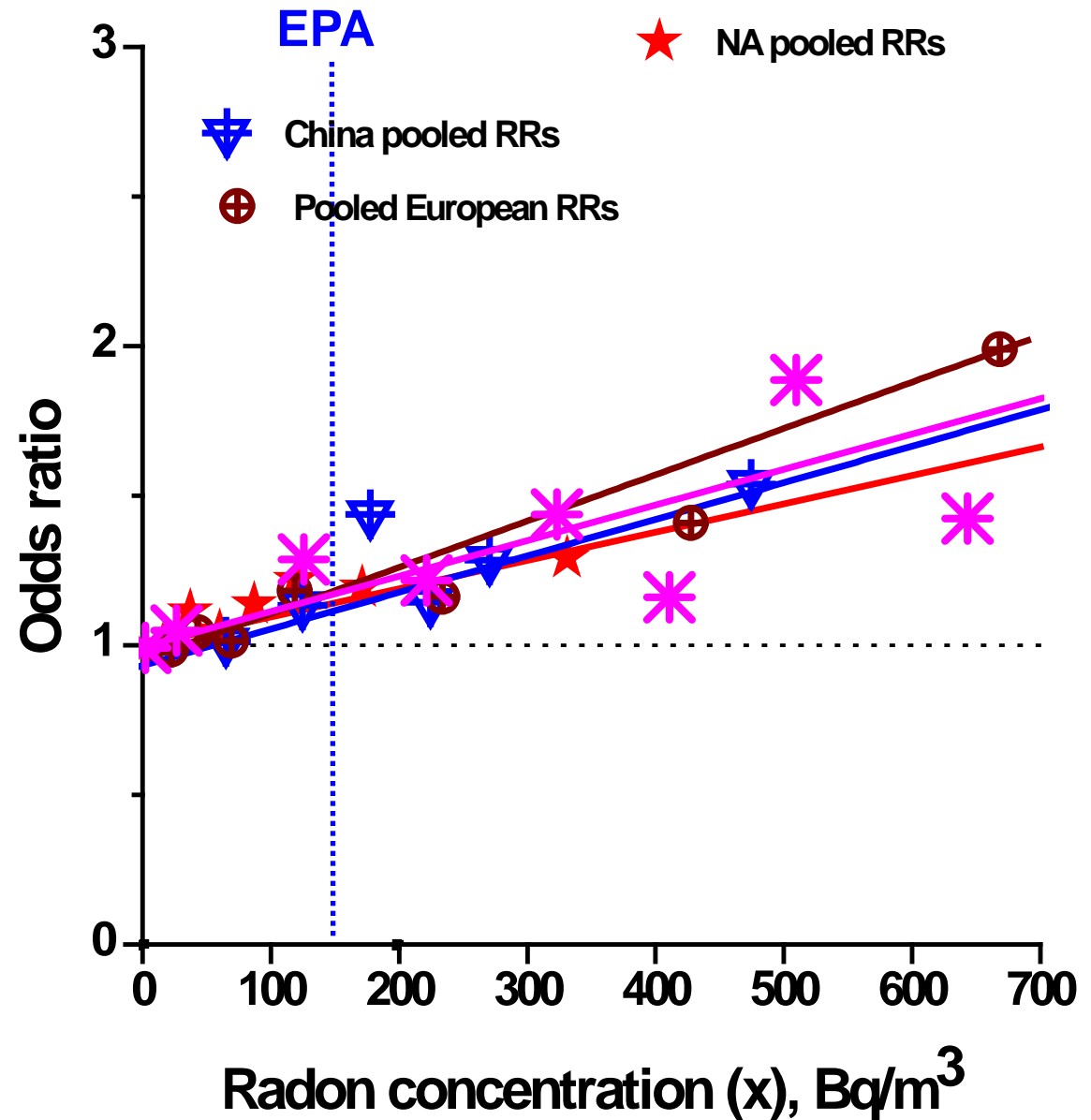
Validity of AR Estimates for Rn-Associated Lung Cancer

- (1) Are miner-based models internally consistent for low-exposed miners?
- (2) Are miner-based models consistent with indoor Rn studies?
- (3) Is there radiobiological/ epidemiological evidence for low-dose effects at indoor Rn levels?

Distribution of radon exposure for cases



Comparability of Results of Indoor Radon Studies of Lung Cancer



Validity of AR Estimates for Rn-Associated Lung Cancer

- (1) Are miner-based models internally consistent for low-exposed miners?
- (2) Are miner-based models consistent with indoor Rn studies?
- (3) Is there radiobiological/epidemiological evidence for low-dose effects at indoor Rn levels?

Cellular studies show that a single alpha particle can cause substantial damage to a cell, which can lead directly or indirectly to adverse chromosomal effects.

Low doses result in at most single particle traversals of cells. Further decreasing dose proportionally reduces the number of cells traversed, but not the degree of insult to a cell.

Cellular studies, radiobiology and epidemiology are consistent with linear dose-response at low doses.

Unanswered Questions for Extrapolating Risk to Indoor Radon

- Do miner-based risk models include all important risk factors?
- Are effect modifiers (smoking, etc.) in miner risk models valid for indoor exposures?
- Do miner-based risk models apply for lifelong exposures at low exposure rates?
- Is the K-factor (≈ 1) correct?
- Are risk models valid for males and for females?
- Do children have any special sensitivity to radon?

Summary

- Miner studies, residential studies, animal studies and radiobiology implicate indoor radon as a cause of lung cancer
- In US, radon may cause 20,500 lung cancer deaths/yr, with a range of 3,000 to 32,000
(2nd leading cause of lung cancer)
- AR greater in never-smokers, but radon-attributable lung cancer deaths greater in ever-smokers
- About 1/3 of AR preventable (148 Bq/m³)
- Due to “low-doses”, estimates always have some uncertainty

Thank You

Areas of Research

epidemiology: world pooling of residential studies

molecular markers: identify markers of exposure,
signature of "radon" lung cancer

cofactor effects: mechanistic formulation of cofactor
effects to guide modeling of epidemiologic data

genomic instability, apoptosis, bystander effects:
effects on dose-response

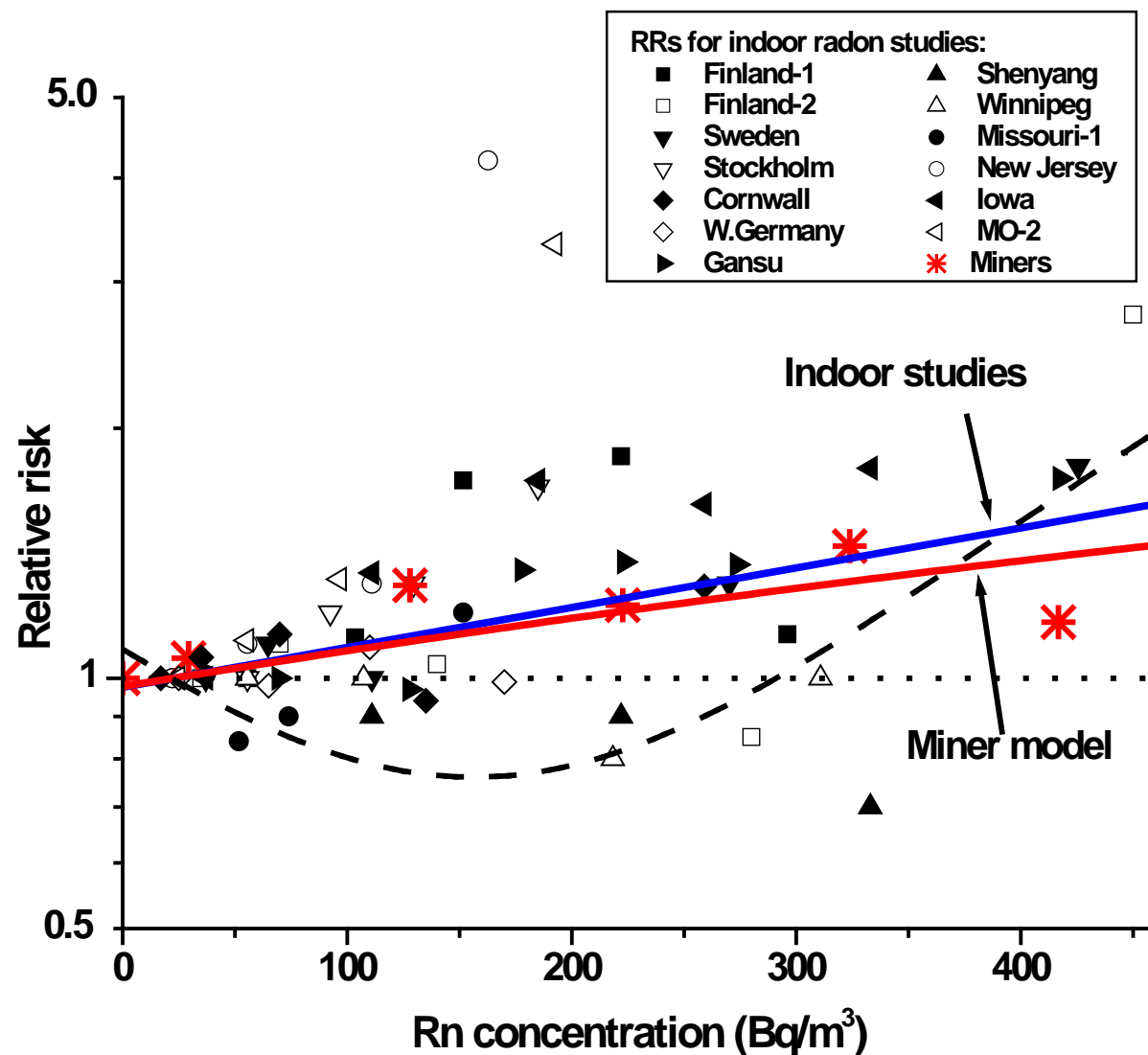
cellular repair mechanisms: improved modeling of
risk reduction with time since exposure

susceptible sub-populations

Ecologic regression of radon

- Limitations of data
- Conditional on cofactors, higher county radon levels DO NOT imply higher county lung cancer rates
- Potential for “ecologic bias” ALWAYS exists
- Adding covariates CANNOT eliminate bias
- Failure of LNT in ecologic regression is irrelevant for evaluating individual risk
- Bias estimation requires within-county population surveys
- Results have NO inferential/evidentiary value

Comparability of Estimates of Radon Risk



Comparing ecological and analytical studies

- Indoor/miner studies linear at low exposures
- Miner studies internally consistent
- Extrapolations from miners agree with indoor studies
- NO study shows a significant “negative” effect for Rn
- Cohen's ecological study shows negative trend $< 200 \text{ bq/m}^3$ and a “protective” effect under 300 bq/m^3

Fundamental problem with ecological studies of R_n

If bias has affected the ecological analysis, then the results must be dismissed, since bias is potentially unbounded. Further, the bias cannot be estimated without data on individuals.

If bias has not affected the ecological analysis, then the negative results make no sense and must be dismissed, since they are at odds with all (20+) analytic studies of individuals, which have much greater validity.